REMARKS

On July 7, 2004, the Applicants filed a Request for Continued Examination (RCE) and a Supplemental Information Disclosure Statement in response to the January 7, 2004, Final Office Action. As a result, claims 18-33 were pending and under examination at the time of the RCE.

In the present communication, the Applicants have amended claims 18-33 in order to further their business interests and the prosecution of the present application, but not in acquiescence to any outstanding rejections or objections. Applicants reserve the right to prosecute the original, or similar, claims in the future. The amendments made to claims 18-33 are fully supported by the specification and the claims as originally filed and do not add new matter. The Applicants have added new claims 34-57 in order to further their business interests and the prosecution of the present application, but not in acquiescence to any outstanding rejections or objections. Newly added claims 34-57 are fully supported by the specification and the claims as originally filed and do not add new matter. Consideration and entry of these amendments and new claims is respectfully requested.

In the Final Office Action mailed January 7, 2004, the Examiner withdrew various rejections over the Costantino *et al.*, Lieberman *et al.*, and Twumasi *et al.*, references as being moot in view of the Applicants' October 14, 2003, communication canceling, without prejudice, claims 1-17. The rejections that were withdrawn are as follows:

1. The rejection of claims 1 and 10, and claims dependent thereon, under 35 U.S.C. § 101 as being directed to a non-statutory subject matter;
2. The rejection of claims 1-8 and 10-16 under 35 U.S.C. § 112, second paragraph, as being indefinite;
3. The rejection of claims 1-3, 5-7, 10, 11, and 13-15 under 35 U.S.C. § 102(b) as being anticipated by Costantino *et al.*, Lieberman *et al.*, Twumasi *et al.*, or Granoff;
4. The rejection of claims 1, 6, 8, 10, 14 and 16 under 35 U.S.C. § 103(a) as being obvious over Granoff; and
5. The rejection of claims 1,4, 10 and 12 under 35 U.S.C. § 103(a) as being obvious over Granoff.

However, the Examiner also made the following new objections and rejections:

1. Claims 22-32 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly containing new matter;
2. Claims 18-33 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite;
3. Claims 18-33 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Chong *et al.* (WO 99/42,130); and
4. Claims 18-33 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Granoff (WO 98/58,670) or Ambrosch *et al.* (Bull. WHO 61(2):317-323 [1983]) in view of André *et al.* (In: Modern Vaccinology, (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, NY, *pp.* 41-54, [1994]) and Levine *et al.* (In: Abstracts of the Tenth International Pathogenic *Neisseria* Conference, (Ed) Zollinger *et al.* Baltimore, MD, *pp.* 228-230 [1997]).

The Applicants will discuss the rejections set forth in the January 7, 2004, Final Office Action in view of the amendments made to claims 18-34.Applicants discussed the currently amended and newly added claims during a telephonic interview on September 3, 2004. The Examiner's time and comments are greatly appreciated.

Applicants respectfully submit that the present amendments and remarks are fully responsive to the Examiner's stated concerns. Accordingly, Applicants respectfully intend for this communication to advance the prosecution of the present application and to place the application in condition for allowance.

1. The Pending New Matter Rejection

Claims 22-32 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter. The Examiner states that bivalent immunogenic compositions having polysaccharides A and C, tetravalent immunogenic compositions having polysaccharides A, C, W135, and Y are clearly disclosed in the present specification. However, the Examiner argues that claims reciting bivalent compositions comprising polysaccharides other than from serogroups –A and –C, and any presently claimed trivalent compositions add new matter. Applicants must respectfully disagree. As mentioned above, Applicants' respectfully submit that newly added claims 34-57 do not add new matter.

Originally filed claim1 was directed to "[a]n immunological composition comprising two, three, or four distinct protein-polysaccharide conjugates, wherein each of the conjugates comprises a capsular polysaccharide from two or more serogroup of *N. meningitidis* conjugated to one or more a carrier protein." Originally filed claim 1 thus encompasses non-A and -C bivalent as well as trivalent immunogenic compositions of *N. Meningitidis* serogroup polysaccharides and is part of Applicant's original disclosure.

Furthermore, as was briefly discussed during the Examiner interview, the Applicants respectfully submit that the instant specification provides additional support for bivalent and trivalent compositions. For example, the specification states that "[t]he present invention provides multivalent meningococcal vaccines comprised of immunologically effective amounts of from two to four distinct protein-polysaccharide conjugates, wherein each of the conjugates contains a different capsular polysaccharide conjugated to a carrier protein, and wherein each of the capsular polysaccharide is isolated from the group consisting of capsular polysaccharide from serogroup A, C, W-135 and Y." (Specification, *p.* 3, ¶ 15; See also, *p.* 4, ¶ 18). One of skill in the art would certainly appreciate the meaning of the phrase "*two to four*" to include compositions of two, three, or four polysaccharides. There is simply no other grammatical interpretation for this phrase. Likewise, there are four potential *N. meningitidis* serogroups from which the skilled artisan is directed to select polysaccharides for use in the

compositions. Notably, both of these clauses are contained in a single sentence. The first clause, "two to four" provides the instruction for selecting polysaccharides from the list included in the second clause, "group consisting of . . ." Thus, the specification clearly teaches compositions comprising 2, 3, or 4 polysaccharides selected from a closed set of four (*i.e.*, A, C, E-135, and Y) candidate polysaccharides. Applicants further note that at page 3, ¶ 16, among other places, the specification clearly recites methods of manufacturing immunogenic compositions comprising from two to four serogroups of *N. meningitidis*.

In view of support found in the specification and the originally filed claims for the subject matter presently recited in the amended/newly added claims, the Applicants must respectfully request that this rejection be withdrawn.

2. The Pending Indefiniteness Rejections

Claims 18-33 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully submit that in view of the Examiner's comments made during the interview on September 3, 2004 and the amendments to claims 18-33 presented herein, that all of the Examiner's concerns have been sufficiently addressed. Accordingly, the Applicants respectfully request that these indefiniteness rejections be withdrawn.

3. The Anticipation Rejection

Claims 18-33 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 99/42,130 to Chong *et al.* (the "'130 publication"). The Applicants must respectfully disagree with the Examiner's arguments for the reasons stated below.

The Federal Circuit has held that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (*Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 [Fed. Cir. 1987]; cited in MPEP § 2131). Applicants respectfully submit that the '130 publication does not teach each and every element of the instantly claimed invention.

The '130 publication is directed to "multivalent immunogenic conjugate molecule[s]" comprising a single carrier protein conjugated to multiple, distinct capsular bacterial polysaccharides or tumor antigens. With respect to infectious organisms, the '130 publication states that the polysaccharides may be selected from different serogroups of a single species of bacteria and/or from one or more distinct bacterial species. In contrast, the instantly claimed compositions relate to distinct polysaccharide-carrier conjugates (e.g., A-carrier, C-carrier, Y-carrier, W-135-carrier) which are individually prepared and

subsequently combined to provide a multivalent immunogenic compositions (e.g., combinations of A-carrier, C-carrier, Y-carrier, and/or W-135 carrier).

The following excerpt from the Summary of the '130 publication provides a general description of the subject matter described therein:

> . . . there is provided a multivalent immunogenic molecule, comprising a carrier molecule containing at least one functional T-cell epitope, and multiple different carbohydrate fragments each linked to the carrier molecule and each containing at least one functional B-cell epitope. ('130 publication, *p.* 9, *ll.* 12-17; emphasis added).

The remaining disclosure of the '130 publication is similarly limited to conjugation of multiple polysaccharides to a single carrier protein (*see e.g.*, *p.* 9, *ll.* 4-9; *p.* 10, *ll.* 17-22 and *ll.* 30-34; *p.* 11, *ll.* 7-10; *p.* 15, *ll.* 19-21; *p.* 15, *l.* 29 to *p.* 16, *l.* 2; *p.* 20, *ll.* 2-7; *p.* 23, *l.* 22 to *p.* 24, *l.* 10; claims 1, 7, 16, 21, and 23; and, Figures 1 and 9). The preparation of the multivalent immunogenic conjugates is described in Examples 1-10. The analysis of the immunogenicity of the multivalent immunogenic conjugates is described in Examples 11-16. Applicants maintain that the '130 publication is completely silent as to the instantly claimed subject matter, which as described above relates to individual immunoconjugates used in combination with one another.

During the interview with the Examiner on September 3, 2004, the Examiner indicated that Figure 9 was, in her opinion, particularly relevant to the instantly pending claims. Applicants respectfully disagree. The specification clearly indicates that Figure 9 relates only to the immunogenicity of a meningococcal multivalent immunogenic conjugate. For example, the figure legend on p. 15, lines 19-21 indicates that the figure is demonstrating "rabbit antibody responses to multivalent N. meningitidis oligosaccharides-TT conjugates . . . ." On page 23, lines 28-31, the '130 publication states that Figure 9 shows "that meningococcal [multiple antigenic glycoconjugate] could elicit antibody responses to all three polysaccharides . . . ." Earlier in the same paragraph, it is stated that the conjugates were prepared using "the procedure shown schematically in Figure 1", which illustrates the conjugation of multiple oligosaccharides to a single carrier protein. Thus, Applicants respectfully maintain that Figure 9 does not relate to instantly claimed conjugates, but instead relates only to the multiple immunogenic glycoconjugates described throughout the '130 publication.

For the reasons stated above, Applicants respectfully maintain the '130 publication does not anticipate the instantly claimed invention and that the instant rejection is improper. Accordingly, Applicants respectfully request that this rejection be withdrawn.

4. The Obviousness Rejection

Claims 18-33 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Granoff (WO 98/58,670) or Ambrosch *et al.* (Bull. WHO 61(2):317-323 [1983]) in view of André *et al.* (In: Modern Vaccinology, (Ed) Kurstak *et al.*, Plenum Medical Book Company, New York, NY, *pp.* 41-54, [1994]) and Levine *et al.* (In: Abstracts of the Tenth International Pathogenic *Neisseria* Conference, (Ed) Zollinger *et al.*, Baltimore, MD, *pp.* 228-230 [1997]). Applicants must respectfully disagree.

The MPEP requires examiners to base obviousness rejections upon three criteria. A valid *prima facie* case of obviousness exists only if the examiner can establish each criterion with sufficient evidentiary support. These criteria prevent the examiner from adopting impermissible and prejudicial attitudes, such as the use of hindsight, during obviousness examinations. MPEP § 2143 *et seq.* describes the three criteria as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings [MPEP § 2143.01]. Second, there must be a reasonable expectation of success. [MPEP § 2143.02] Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations [MPEP § 2143.03].

The Applicants respectfully submit that the Examiner has not made a valid *prima facie* case of obviousness because she has not sufficiently established the requisite criteria.

The Examiner's stated rational for combining Granoff, Ambrosch, Andre, and/or Levine is as follows:

> Given the art-recognized disadvantages of the U.S.-licensed quadravalent or tetravalent meningococcal Menomune® polysaccharide vaccine comprising serogroup A, C, Y and W135 meningococcal capsular polysaccharides as taught by Granoff ('670), including their poor immunogenicity in children less than 2 years of age as also taught by Ambrosch et al., it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to conjugate the individual serogroup A, C, Y and W135 meningococcal capsular polysaccharides present in the Menomune® polysaccharide vaccine disclosed by Granoff ('670) to the art-known protein carrier, non-toxic diphtheria toxin mutant, CRM197, using art-known conjugation technology to produce the instant invention with a reasonable expectation of success, because Andre et al. expressly suggested conjugate vaccines as the answer to the problem of poor immunogenicity, and Levine et al. expressly taught that routine infant immunization with a quadrivalent meningococcal polysaccharide A, C, Y and W-135-protein conjugate vaccine is likely to have a substantial impact on endemic meningococcal disease and may provide herd immunity. (Office Action, *pp.* 7-8; emphasis added).

The Examiner is apparently arguing that the deficiencies in Granoff are satisfied by André *et al.* and/or Levine *et al.*, and that André *et al.* and/or Levine *et al.* provide the motivation and the reasonable

expectation of success to modify the state of the art tetravalent (*i.e.*, unconjugated meningococcal capsular polysaccharides A, C, Y, and W135) polysaccharide vaccine described by Granoff or Ambrosch *et al.* to derive the presently claimed polysaccharide-carrier immunogenic conjugates. More particularly, the Examiner argues that Granoff describes deficiencies in the MENOMUNE® vaccine, and that Andre *et al.* and/or Levine *et al.* provide the motivation to produce a conjugated meningitis composition in order to satisfy those deficiencies. Granoff, Andre *et al.*, and Levine *et al.* merely set forth the examiner asserted art-recognized deficiencies in the MENOMUNE® vaccine and the art-recognized desire for new compositions for immunizing humans against *N. meningitidis*. However, it must be emphasized that a conjugated product at best was recognized by industry as only a *potential* solution to the problem. Furthermore, the references provide no guidance on how to achieve such a product.

Accordingly, Applicants respectfully submit that the cited references at best provide a motivation to *try* to develop a product that cures the deficiencies of the MENOMUNE® vaccine. It appears, then, that the Examiner's rejection is based upon an "**obvious to try**" rationale for modifying and/or combining references during the obviousness examination. The Federal Circuit has repeatedly stated that using an "**obvious to try**" rational is a legally impermissible basis for attempting to establish a motivation to combine references especially in unpredictable fields such as immunology and vaccinology[1].

The Examiner argues that there were art-recognized deficiencies in the then-available polysaccharide vaccines (i.e., MENOMUNE® tetravalent polysaccharide vaccine). The Applicants agree with the Examiner on the point that Andre *et al.* and Levine *et al.* discuss the economic benefits that **might** be derived from a meningococcal conjugate vaccine. However, while the combination of these references may emphasize the need for or desire for new immunogenic compositions, none of Granoff, Ambrosch *et al.*, Andre *et al.*, or Levine *et al.* provide any reasonable expectation of success in constructing and using the instantly claimed invention.

Applicants note that Granoff provides a general description of an "anti-meningococcal glycoconjugate vaccine composition" on page 11 (lines 13-19) and a list of specific conjugates on page 12

[1] "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." (*In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 [Fed. Cir. 1999]; emphasis added). "Obvious to [try] is not a proper standard for obviousness. . . . [S]elective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings." (*In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 [Fed. Cir. 1988], emphasis added). "An 'obvious to try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." (*In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 [Fed. Cir. 1990]; emphasis added).

(lines 22-34). In this specific list, Granoff fails to even mention the possibility of *N. meningitidis* serogroup Y and/or W-135 polysaccharide-carrier conjugates. Granoff, however, does provide a lengthy discussion of the serogroups that would be useful in polysaccharide-carrier conjugate, namely, serogroups A, B, and C. Granoff is completely silent as to the use of serogroups Y and W-135 in a conjugate. The Examiner admits this by saying that "[t]he teachings of Granoff ('670) or Ambrosch *et al.* . . . do not expressly disclose that A, C, Y and W135 meningococcal capsular polysaccharides in their multivalent meningococcal vaccine are conjugated to one or more carrier proteins." (Final Office Action, *p.* 6). Granoff's omission of serogroups W-135 and Y is conspicuous and significant given: 1) the Examiner's assertion of art-recognized deficiencies in the MENOMUNE® vaccine; 2) Granoff's description of the state of the art tetravalent vaccine at the time (i.e., MENOMUNE®) as including the Y and W-135 polysaccharides; and 3) the call in André *et al.* and Levine *et al.* for A, C, Y, and W-135 tetravalent anti-meningococcal vaccines. Notably, the André *et al.* reference predates Granoff by three years, while the Levine *et al.* reference is a 1997 contemporary of Granoff. This begs the following question: why did Granoff (considered by many to be an expert in the field of *N. meningitidis*) fail to even mention the possibility of polysaccharide-carrier conjugates comprising serogroups W-135 and Y? Applicants respectfully submit that Granoff did not mention serogroup W-135 and Y polysaccharide-carrier conjugates because there was no **reasonable expectation** of successful making and using these compositions prior to the present invention.

Neither André *et al.* nor Levine *et al.* satisfy the deficiencies apparent in Granoff and Ambrosch *et al.* Indeed, André *et al.* state that serious unresolved doubts surrounded the use and development of anti-meningococcal polysaccharide-carrier conjugates. For example, André *et al.* state that:

> "Conjugate vaccines **could** be the answer to these problems [the problems asserted as being inherent in polysaccharide vaccines]. The persistence of protective antibodies induced by these vaccines [meningococcal polysaccharide-carrier conjugates] **is also in doubt**, which may result in revaccination of children living in endemic areas becoming a necessity." (André, *p.* 45, *ll.* 13-16; emphasis added).

Thus, Applicants submit that while Andre *et al.* suggested that the industry **try to make** a meningococcal conjugate, Applicants must respectfully disagree with the Examiner's statement that André *et al.* "expressly suggested conjugate vaccines" in a manner consistent with a proper obviousness analysis. At best, André *et al.* might "**pique the interest**" of one skilled in the art to **try to make** immunogenic *N. meningitidis* polysaccharide-carrier conjugates. Applicants note again, however, that this an insufficient basis for establishing a motivation for combining references. Andre's discussion, alone or in combination with the other cited references, does not provide any reasonable expectation of success in producing or

using the instantly claimed invention. The expectation of success only appeared following Applicants' actual manufacture of the conjugate and testing of the conjugate in human beings.

Levine *et al.* provides a purely economics based cost–effectiveness (C-E) decision model, "using the societal perspective, that compares the costs and benefits from routine infant immunization to the costs and benefits from the current situation where no routine infant immunization exists.". (Levine *et al.*, *p.* 228, ¶ 2). Levine *et al.* focus on the asserted public health benefits of infant vaccination in the U.S. with a tetravalent *N. meningitidis* polysaccharide-protein conjugate as a means of decreasing costs associated with meningococcal disease. It is important to note, however, that no such infant vaccine or vaccination program existed as of Levine's publication date, accordingly, Levine *et al.* is forced to rely on several unsupported assumptions for his analysis. First, Levine's C-E model is not based upon any data in any age group describing the administration of a tetravalent meningococcal polysaccharide-carrier conjugate in humans because before the present invention none existed. Second, Levine *et al.* inexplicably fail to provide any teaching or guidance on how to make, store, administer, monitor, and so forth, any immunogenic composition, no less the immunogenic compositions they purport to model. Levine's authors themselves recognize that their C-E model is based on **unsupported** scientific and economic assumptions. For example, Levine *et al.* state that:

> "[t]he C-E MenConj vaccine in this analysis is based on **some important assumptions.** First, it must be administered in the same syringe with the Hib conjugate vaccine (or other appropriate vaccine), thereby eliminating costs for additional visits or equipment to store and administer the vaccine. Second, we assume that the vaccine will provide 90% protection for at least 4.5 years." (Levine *et al.*, *p.* 229, ¶ 5, emphasis added).

There is no basis for Levine's assumption that anti-meningococcal polysaccharide-carrier conjugates would be 90% protective for at least 4.5 years or even that four meningococcal capsular polysaccharide-carrier conjugates would be immunogenic and non-reactogenic when combined given the unpredictable nature of vaccinology. Likewise, there is no basis for Levine's assumption that such an immunogenic composition, if it could be made, could be combined with a Hib conjugate vaccine without side effects such as reactogenicity and/or efficacy issues (*e.g.*, carrier induced epitopic suppression, component precipitation, *etc.*). In sum, Levine *et al.* fails to provide any explanation as to why the assumptions it relies upon are valid or even feasible.

Given Levine's many shortcomings, there is no reason to believe that one skilled in the art would have had a reasonable expectation of successfully making and using the presently claimed polysaccharide-carrier conjugates. As with Granoff, Ambrosch *et al.*, and Andre *et al.*, Levine *et al.* may speak to the desirability of such compositions, but it fails to provide any guidance on how these compositions could be made or used, or how combine its teachings could possibly be combined with any

other reference. Accordingly, Applicants must respectfully submit that the Levine's C-E model is unsupported conjecture.

None of the references provide any indication that the presently claimed immunological compositions—if successfully made—would reasonably be expected to be protective. In fact, as mentioned above, several of the references undermine this assumption. It is only in view of the Applicants' clinical success that the Examiner using hindsight can argue that such compositions could reasonably be expected to be protective. This is especially true in view of the teachings in Granoff and André *et al.* regarding the development and administration of tetravalent anti-meningococcal polysaccharide-protein conjugates.

In summary, Applicants believe that the Examiner has failed to demonstrate the cited references provide the motivation to modify or combine the references to produce the instantly claimed invention with any reasonable expectation of success. For the reasons stated above, and for those previously made of record, Applicants respectfully request that this rejection be withdrawn.

5. New Claims 34-54

Claims 34-57 each, respectively, depend from newly added claim 34. Briefly, newly added claims 34-37 are directed to certain embodiments of the present invention comprising non-proteinaceous adjuvants. Newly added claims 38-45 are directed to certain embodiments of the present invention comprising particular ranges, in micrograms, of capsular polysaccharides and carriers. Newly added claims 46-50 are directed to certain embodiments of the present invention comprising proteinaceous adjuvants. Next, newly added claims 51-55 are directed to certain embodiments of the present invention comprising particular formulations and composition packaging schemes. Finally, newly added claims 56 and 57 are directed to certain embodiments of the present invention comprising preservatives. Applicants respectfully submit that since claims 34-57 are each based on allowable base claims, it follows that claims 34-57 are also allowable.

6. Conclusion

Applicants respectfully request entry of this communication and reconsideration of the instant pending claims in view of the amendments and remarks presented herein. Applicants believe that the amendments and remarks presented herein have more are more than sufficient to overcome all of the Examiner's stated grounds for rejecting and objecting to the instant pending claims. Thus, Applicants respectfully request issuance of a timely Notice of Allowance in this application. Should the Examiner

have any questions concerning this application, she is invited to contact the undersigned collect at (570) 895-3036.

Respectfully submitted,

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